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Role of Pharmacovigilance in Drug Discovery & Post-Marketing Surveillance

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ABSTRACT

Pharmacovigilance is a cornerstone of both the pharmaceutical industry and the healthcare system. It is aimed to ensure guaranteed patient safety and is considered an arm of patient care. Pharmacovigilance is essential at many stages of the drug discovery and development process. Drug safety assures that a patient's safety and well-being are protected throughout the whole drug development lifecycle, including when the drug is easily available on the market. Pharmacovigilance comprises pre- and post-marketing surveillance. Pre-clinical screening, which collects information on ADRs from phases I to III of clinical trials, and post-marketing surveillance, which gathers data from the post-approval stage and during the course of a drug's shelf life. During clinical trials pharmacovigilance mandates the timely submission of reports on adverse events during clinical trials to regulatory authorities, notification of such events to all investigators and ethics committees, and a safety review by independent Drug Safety Monitoring Boards (DSMB). Predicting or evaluating potential ADRs at this early stage of the drug development pipeline is the focus of PV. Finding previously unrecognized adverse effects as well as good effects is the major goal of PMS research by utilizing various pharmacovigilance methodologies.

KEYWORDS: *Pharmacovigilance, ADRs, clinical trials, post-marketing surveillance*

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INTRODUCTION

Health includes not only being disease-free but also being in good bodily, psychological, and social health. The treatment of the sickness is the first step towards achieving a state of balance. Such treatment necessitates the categorical requirement that the medication used to treat the disease does not hurt the patient in a way that further reduces the quality of life or causes death.

This vigilance in finding out all aspects of a drug, positive and negative, has led to the evolution of a new branch of pharmacological science, known as Pharmacovigilance. It is one of the fundamental wings of the healthcare system and pharmaceutical companies. It is aimed to ensure guaranteed patient safety and is considered an arm of patient care.

The Australian physician W. McBride, who first hypothesized a connection between thalidomide, a medication used during pregnancy, and severe fetal abnormalities (phocomelia), officially established pharmacovigilance (PV) in December 1961 with the publication of a letter(case report) in the Lancet: In pregnant women, thalidomide was administered as a sedative and antiemetic.[1]

The French word pharmacovigilance was defined as "a discipline involving detection, evaluation, and prevention of undesirable effects of medicines." This word derives from the Greek "pharmakon," which means a drug or remedy, and the Latin "vigilans," which means attentive or careful. By the World Health Organisation (WHO), pharmacovigilance is "the science and activities related to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem." [2]

Patient safety and ongoing monitoring

By definition, drug safety assures that a patient's safety and well-being are protected throughout the whole drug development lifecycle, including when the drug is easily available on the market. Patients' reactions to medications are constantly being watched for additional adverse effects, and any fresh

information is regularly gathered and reported to regulatory bodies for medical care. No other department has such a keen focus on enhancing patient lives in everything they do, in contrast to other sectors.

To centralize global data on adverse drug reactions (ADRs), the World Health Organisation (WHO) developed the "Programme for International Drug Monitoring" in 1968. The "WHO Programme" in particular sought to locate the earliest PV indications. [1]

Pre- and post-marketing surveillance are two stages of PV that include pre-clinical screening, which gathers data on ADRs from phases I to III of clinical trials, and post-marketing surveillance, which gathers information from the post-approval stage and during the course of a drug's shelf life. [3]

The high prevalence of mortality and morbidity worldwide is largely attributed to adverse drug reactions (ADRs), and the safety of medically connected items is prioritized over their efficacy. Therefore, to protect patients, regulatory bodies around the world mandated that all medium-sized and large-scale pharmaceutical enterprises have effective PV systems. The need for worldwide pharmacovigilance is being driven by a rise in the prevalence of chronic diseases, research and development, and clinical trials.

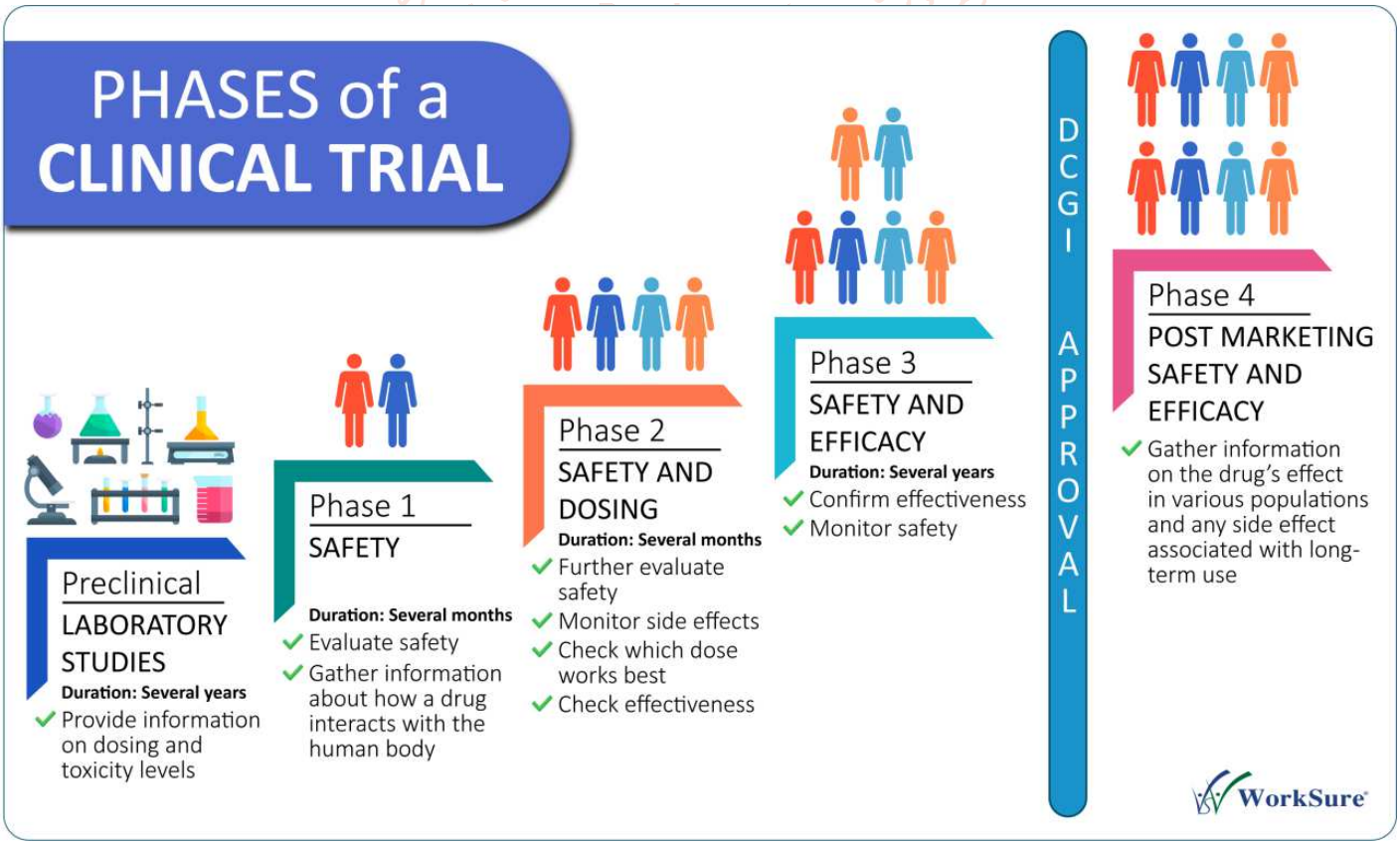
An ADR is defined by the World Health Organization (WHO) as a response to a drug that is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease or the modification of physiological function'.

The Purpose of Pharmacovigilance :

The scope of pharmacovigilance has been widened to include:[2]

- Herbal preparations
- Traditional and complementary medicines
- Blood products
- Biologicals
- Medical devices
- Vaccines

The process of creating a new medicine starts with the identification of a potential pharmacological agent and continues via regulatory approval, efficacy and safety research, and testing. Phase I, II, III (pre-marketing), and IV (post-marketing) trials are the key components of the medication approval process. Pre-marketing research inevitably involves controlled settings and a predetermined population. Even though these trials give the impression that a new drug is safe, when it is made available for use by the general public, unanticipated negative effects may develop.



The process of finding and developing new drugs is protracted, expensive, competitive, and difficult. It takes several years of work to bring a medicine from the bench to market, from screening and identification of the drug to its release onto the market. A novel drug's discovery and development requires complex interactions

between industry, academics, investors, regulatory agencies, marketing, and the need to strike a balance between confidentiality and communication. Drug research, drug development, regulatory review and approval, and marketing are the four processes that make up the entire process of introducing medicine to patients The ability to administer the appropriate medicine dose to the appropriate patient is a crucial component of therapeutics.

Choosing and establishing a "safe dose" is a process that happens throughout a drug's clinical development. The fundamental determinant of a medicine's safety is the dose that is provided, and establishing a safe and effective range is one of the main goals of clinical drug development.

Drug discovery:
The first step in the drug discovery process is to find a suitable "druggable" target, which can be a biomolecule or a protein receptor that is specifically linked to a pathology or disease condition. The next stage after identifying a target is to validate it and determine its involvement in the development of the disease. The target is then tested against a variety of small-molecule drugs to find possible leads that interact with the target biomolecule and have the potential to stop or delay the progression of the disease.

Drug development:
The drug development phase entails thorough testing and optimization of the chosen compounds to find the 'drug candidate' that might be the most successful in terms of safety, toxicity, dose, and efficacy. To examine their pharmacodynamic and pharmacokinetic features, which include Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADME/Tox) capabilities, the chosen lead compounds are evaluated in cells (in vitro) and in animals (in vivo) for this purpose. The ideal lead candidate should not be toxic, be able to enter the bloodstream, be delivered to the right location inside the body, and be successfully metabolized as well as removed from the body.

The 'preclinical phase' of the drug development process is when the potential drug is carefully reviewed, improved, and ready for testing on humans. The 'clinical phase' of development follows this stage, during which a drug candidate's safety and efficacy are evaluated in human test subjects. The three stages of this "clinical trial" are: Phase 1 entails preliminary human testing in a small number of healthy volunteers, Phase 2 entails testing in a small number of patients, and Phase 3 entails testing a large number of patients to demonstrate the safety and efficacy of the drug candidate in them because healthy and ill people may have different metabolic patterns for the drugs.

Regulatory review and approval:
The results of the 'clinical trial' determine whether the drug candidate is secure and sufficient in treating the illness. The United States Food and Drug Administration (USFDA), which is responsible for the development, approval, and marketing of medicines, is one regulatory authority that may receive new drug applications with all necessary evidence, including high-quality preclinical and clinical data gathered during the development of the drug candidate. they must accept the drug applications before the business can market the medication in their regions (e.g., a New Drug Application (NDA) in the US and a Marketing Authorization Application (MAA) in Europe).

Commercialization:
The drug development process ends at this stage. Following approval, the medication is marketed or commercialized. In each country where they intend to sell the drug, the drug producers must submit applications for marketing permission.

medicine research and development often take between 10-15 years, cost between $0.8 and $1 billion per medicine, and have a relatively high attrition rate for novel treatment candidates in the clinical stage.[4] To address the problems associated with the failure of new pharmaceuticals, the USFDA launched the "Critical Path Initiative and the Critical Path Opportunity" program in 2004 to direct the development process of a new drug.[5]

Role of pharmacovigilance in drug discovery:
At different stages of the drug discovery and development process, pharmacovigilance is crucial. For instance, in clinical research, pharmacovigilance mandates the timely submission of reports on adverse events during clinical trials to regulatory authorities, notification of such events to all investigators and ethics committees, and a safety review by independent Drug Safety Monitoring Boards (DSMB). Annual reports, an overview and analysis of all significant adverse events, fresh safety results from animal research, and assessments of the benefits versus drawbacks are also necessary.

Predicting or evaluating potential ADRs at this early stage of the drug development pipeline is the focus of PV. One of the essential techniques is the use of preclinical in vitro Safety Pharmacology Profiling (SPP) by evaluating substances using biochemical and cellular assays. According to the theory, if a substance binds to a certain target, its action may translate into the potential occurrence of an ADR in people.[6]

However, in terms of cost and effectiveness, experimental ADR detection is still difficult. Developing computational methods to anticipate probable ADRs utilizing preclinical properties of the drugs or screening data has been the subject of various research projects.

When the medication is sold, pharmacovigilance also plays a big part. Companies in the marketing phase are required to report safety reviews. These safety evaluations include Risk Management Plan (RMP), Periodic Benefit Risk Evaluation Report (PBRER), the Development Safety Update Report (DSUR), [7] Periodic Safety Updates Report (PSUR),[8] phase 4 studies (post-marketing surveillance), clinical trials (intervene disease management), and pharmacoepidemiological studies (noninterventional or observational).

A crucial and unavoidable step in the process of discovering new drugs is pharmacovigilance. Every stage of drug development will need thorough documentation and strict supervision, including pharmacovigilance inspection and audit, risk management, reporting of ADR medications, routine safety update reports, post-authorization safety studies, more oversight, and safety communication. therefore, it is crucial to establish good pharmacovigilance practices for enhancing understanding of drug safety issues during drug development and post-approval so that attrition rates can be reduced and the patients can be provided with safe and effective innovative medicines to meet their prerequisite medical needs.

Post-marketing surveillance:

Following licensure, research tends to continue on the safety of novel medications for human ingestion. These investigations are often known as "phase IV trials" or "post-marketing studies." Post-marketing surveillance (PMS), to put it simply, is the practice of keeping an eye on a drug's safety after it is approved for marketing by a regulatory body and after completing clinical studies. Finding previously unrecognized negative consequences as well as beneficial benefits is the main goal of PMS research. Off-label drug use, orphan drug challenges, and difficulties with conducting international clinical trials in children can all be considered crucial elements as well.[9]

In the UK, 176 out of every 100,000 persons reported an adverse incident in 2013.4 Similar to the United States,[10] Canada reports over 200,000 ADRs annually, up to 22,000 of which result in reported deaths. Only reported ADRs were included in these numbers, although it's well-accepted that 90% of ADRs don't get reported.

Even when a drug is thoroughly examined before the Food and Drug Administration (FDA) approves it, many adverse drug reactions (ADRs) may still go undetected since clinical studies are frequently small, brief, and biased by excluding patients with concomitant conditions. Premarketing trials do not accurately represent real clinical use scenarios for various populations (like inpatients), hence it is crucial to maintain post-market surveillance.

PV is crucial to the post-market evaluation of recently produced medications. Before a new drug is introduced to the market, an intricate research and development process is facilitated by competition among pharmaceutical companies and strict regulatory evaluation procedures. Post-marketing PV can be obtained from a variety of distinctive data sources. [1]

Only a limited amount of information on uncommon ADRs will be available from the safety and efficacy assessments of any new medical product conducted during clinical trials. In addition, the post-marketing phase is typically the only time that "rare" and "very rare" ADRs are discovered (1 in 1000 and 1 in 10,000, respectively). This is mostly due to the limited variety of disorders, referred to as the "five toos: too few, too simple, too narrow, too median-aged, and too brief," which refers to the limited patient selection criteria, sample size, and small clinical study period.

Pharmacovigilance and pharmacoepidemiology are two areas of pharmacology that are addressed by post-marketing drug monitoring activities. The primary goal of pharmacovigilance sometimes referred to as drug safety surveillance, is the "timely detection" of "novel" ADRs that are distinct in their "clinical nature, severity, and/or frequency." The "population-based study of drug use and the risks associated with that use" is known as pharmacoepidemiology. The importance of pharmacovigilance should be promoted by emphasizing that a drug's

real life begins when it is put on the market. Due to advancements in technology, PMS can now be actively managed with the aid of computers and electronic medical devices. [11]Analyse how the Medicines and Healthcare Products Regulatory Agency (MHRA) in the UK and Health Canada in Canada are likely to show similarities and disparities in the way the PV systems are regulated. Review the specific components and processes involved in the reporting of adverse events.

The World Health Organisation (WHO) defines "signals" as "undisclosed assertions on direct relationships between effects on the human organism and a drug to induce adverse events". To generate comprehensive signal datasets, clinicians and researchers use spontaneous reporting systems (SRS), which are already in use in some European nations and the United States.

Table 1. Examples of medicines with serious ADRs identified during the post marketing period.

Drug	Examples of ADRs identified through post-marketing reports
Amisulpride[28]	Torsades de pointes
Cyamemazine[28]	Torsades de pointes
Olanzapine[28]	Torsades de pointes
Benfluorex[30]	Valvular heart disease
Pergolide[31]	Increased incidence of cardiac valvulopathy
Hydromorphone hydrochloride extended-release[32]	Dose dumping with alcohol, which leads to accidental overdosing
Cisapride[33]	Palpitations, tachyarrhythmias, torsades de pointes, ventricular fibrillation, QT prolongation, sudden death
Rosiglitazone[34]	Fluid retention and congestive heart failure

ADR, adverse drug reaction

Spontaneous reporting:

A spontaneous report is an unsolicited communication made to a company, regulatory body, or other organization by consumers or healthcare professionals that details one or more adverse drug reactions (ADRs) in a patient who has taken one or more medications and that is not the result of a study or other formalized data collection process. After a medicine is marketed, spontaneous reports are crucial in identifying safety signs. A corporation can frequently be informed about uncommon adverse occurrences that were missed in prior clinical trials or other pre-marketing investigations. [12]

An essential method for acquiring safety data for early detection is the spontaneous reporting of ADRs and adverse events. Case reports gathered by such a system serve as the information source with the lowest degree of evidence and the highest level of causation uncertainty. Spontaneous reporting offers benefits in that it is available right away once a new medicine is released, lasts forever, and includes all patients taking the medication. It typically produces safety signals that need to be further investigated and is the way most likely to find novel, uncommon ADRs.

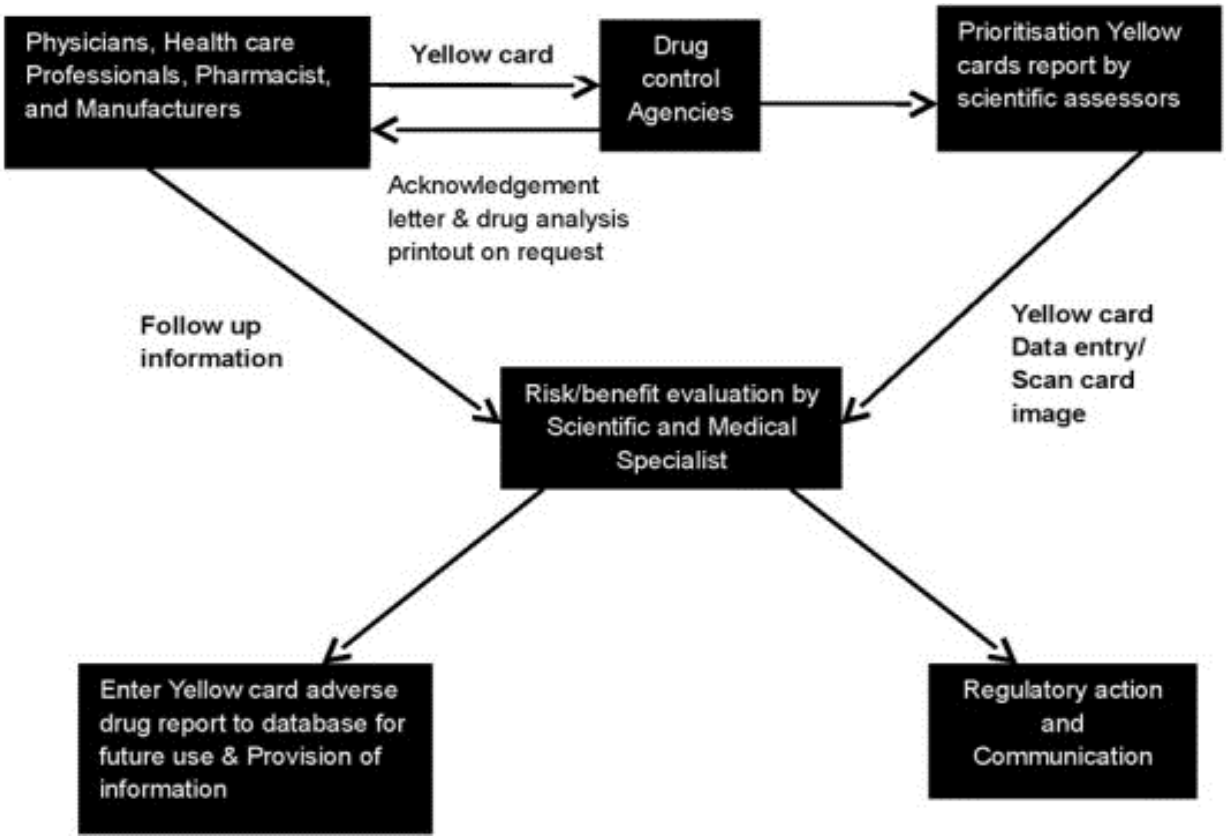
Yellow Card Scheme: The Yellow Card program, which is jointly run by the MHRA and the Committee of Human Medicines (CHM), is how PMS or pharmacovigilance is practiced in the UK. One of the earliest PV programs designed to reduce ADRs is known as the Yellow Card program.[13]

The following goals are covered by PV:[14]

- Monitoring the usage of medications in daily practice to spot previously undetected ADRs as well as changes in the patterns of adverse effects.
- Conducting risk-benefit analyses for medications and recommending appropriate steps, if and when required.
- Providing regular updates to healthcare professionals and patients about the safe and efficacious use of medicines.

Yellow card schemes (YCS) were applied to spontaneous reporting systems. As a result of the thalidomide disaster, it was founded in 1964. Since that time, the system has grown to be a significant international PV resource. The Yellow Card scheme is run jointly by the Medicines Control Agency (MCA) which is the regulatory agency and the Committee on Safety of Medicines (CSM) which is the expert committee. Since 1991,

the YCS has been enhanced by a new computer system, the ADROIT (Adverse Drug Reaction Online Information Tracking) system. ADROIT is different from other databases. It stores not only the report's specifics but also a picture of the yellow card in the optical system. Any yellow card displayed on the screen may be viewed simultaneously by many individuals. The reports are ranked to ensure that major medication reactions are addressed right away.



Adverse drug reactions online information tracking and yellow card system Sources of data

Detection and reporting:

PV center receives a report of suspected ADRs involving one or more medicinal products from a healthcare professional or marketing authorization holder. Reports can be submitted on paper report forms, over the phone, online, or by any other means that have been permitted. The PV center gathers and verifies reports, which are then often recorded into a database. The highest attention should be given to handling serious reactions. The database is utilized to find potential signals and analyse information to understand risk variables, apparent changes in reporting profiles, etc. Systematic techniques have been applied to identify safety signals in spontaneous reporting.

A pattern that might indicate the potential signal is evaluated by experts as they examine each report individually. A signal is frequently produced by a collection of observations from diverse observers rather than a single report because a single report may not always be conclusive. Since the signal is merely a cautionary indication rather than concrete proof of a potential relationship, more research will be needed to either support or refute it.

Pharmacovigilance methods:

As per International Conference on Harmonization Efficacy Guideline 2 ICHE2E guidelines, the pharmacovigilance methods can be categorized as[2]:

- Passive surveillance
  - Spontaneous reporting system (SRS)
  - Case series
- Stimulated reporting
- Active surveillance
  - Sentinel sites
  - Drug event monitoring
  - Registries
- Comparative observational studies
  - Cross-sectional study (survey)
  - Case-control study
  - Cohort study
- Targeted clinical investigations
- Descriptive studies
  - Natural history of the disease
  - Drug utilization study

Pharmacovigilance methods can be also classified as hypothesis generation methods and hypothesis testing methods.

Hypothesis generating methods
- Spontaneous ADR reporting
- Prescription event monitoring

Hypothesis testing methods
- Case-control study
- Cohort studies
- Randomized controlled trials.

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Conclusion:

This is an overview of the two departments where pharmacovigilance is used. For the efficient use of medications and the provision of high-quality medical care, safety monitoring is a crucial component. ARDs considerably reduce safety, lengthen hospital stays, and lower quality of life, all of which lead to a rise in mortality and morbidity. PV focuses on anticipating or assessing probable ADRs at this early stage of the drug development pipeline. The fundamental tenet of PMS and PV is that patient safety and health are important considerations in the development and marketing of pharmaceutical goods. PMS completes the post-approval of the medication. In addition to possible hazards, previously unidentified adverse responses can be found when using medications.

References:

[1] Suke SG, Kosta P, Negi H. Role of pharmacovigilance in India: An overview. Online journal of public health informatics. 2015;7(2.

[2] Mulkalwar S, Worlikar PS, Munjal N, Behera L. Pharmacovigilance in India. Medical Journal of Dr. DY Patil University. 2013 Apr 1; 6(2):126-31.

[3] Berlin JA, Glasser SC, Ellenberg SS. Adverse event detection in drug development: recommendations and obligations beyond phase 3. American journal of public health. 2008 Aug; 98(8):1366-71.

[4] Agrawal P. Drug discovery and development: an insight into Pharmacovigilance. Journal of Pharmacovigilance. 2014 Jun 27.

[5] U.S. Department of Health and Human Services (2004) Innovation or Stagnation: Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products. Food and Drug Administration.

[6] Whitebread S, Hamon J, Bojanic D, Urban L. 2005. Keynote review: in vitro safety pharmacology profiling: an essential tool for successful drug development. *Drug Discov Today*. 10, 1421-33. 10.1016/S1359-6446(05)03632-9

[7] Department of Health and Human Services (2003) Safety Reporting Requirements for Human Drug and Biological Products, Food and Drug Administration.

[8] Klepper MJ. The periodic safety update report as a pharmacovigilance tool. Drug Safety. 2004 Jul; 27:569-78.

[9] Vlahović-Palčevski V, Mentzer D. Postmarketing surveillance. Pediatric clinical pharmacology. 2011:339-51.

[10] unevicius R, Haagsma JA. Incidence and mortality from adverse effects of medical treatment in the UK, 1990–2013: levels, trends, patterns, and comparisons. International Journal for Quality in Health Care. 2018 Aug 1; 30(7):558-64.

[11] Alomar M, Tawfiq AM, Hassan N, Palaian S. Post-marketing surveillance of suspected adverse drug reactions through spontaneous reporting: current status, challenges, and the future. Therapeutic advances in drug safety. 2020 Aug;11:2042098620938595.

[12] Kurz X, Slattery J, Addis A, Durand J, Segec A, Skibicka I, Szmigiel A, Hidalgo-Simon A. The Eudra Vigilance database of spontaneous adverse reactions as a tool for H1N1 vaccine safety monitoring. In Pharmacoepidemiology and Drug Safety 2010 Aug 1 (Vol. 19, pp. S330-S331). 111 RIVER ST, HOBOKEN 07030-5774, NJ USA: WILEY-BLACKWELL.

[13] Gupta SK. Drug discovery and clinical research. JP Medical Ltd; 2011.

[14] Raj N, Fernandes S, Charyulu NR, Dubey A, GS R, Hebbar S. Postmarket surveillance: a review on key aspects and measures on the effective functioning in the context of the United Kingdom and Canada. Therapeutic advances in drug safety. 2019 Jul; 10:2042098619865413.